

From the Section of Allergy of the Department of Microbiology and Immunology of the Medical School of São Paulo—and (la. Cl. Méd.) of the “Hospital das Clínicas”, Medical School of São Paulo. Head: Ernesto Mendes, M.D.

ACTION OF PREDNISONE¹, ON EXPERIMENTAL ASTHMA OF THE GUINEA PIG

By

ERNESTO MENDES

(With technical assistance of A. Germano da Silva)

The respiratory symptoms produced in sensitized guinea pigs afterwards submitted to inhalations of the specific antigen were called by *Ratner* (17) “respiratory anaphylaxis”. This author believed that those symptoms had sufficient analogy with the human asthmatic syndrome, and he preferred to name them “experimental asthma”.

Kallos and *Pagel* (13) concluded also that inhalation of the homologous antigen elicits in the allergic guinea pig attacks which clinically,—roentgenologically, pharmacologically and immunologically simulate human bronchial asthma.

According to *Malkiel* (15), ACTH and cortisone do not protect guinea pigs against fatal anaphylaxis, in spite of the great alleviation of symptoms obtained with these hormones in human asthma. *Feinberg et al.* (5) have demonstrated that ACTH and cortisone markedly inhibit experimental asthma in guinea pigs passively sensitized with aerosol of crystallized ovalbumine. A similar inhibitory effect was questionable in the bronchospasm of the guinea pig due to an aerosol of histamine.

¹ Meticorten from Schering S.A.

The present study was conducted in order to investigate and evaluate the action of *Prednisone* on the experimental asthma of the guinea pig and on the histamine produced bronchospasm of the same animals.

MATERIAL AND METHODS

Guinea pigs weighing from 450 to 500 g were employed in this study. The animals were put into a special glass chamber, with the capacity of 18 liters, and submitted to an aerosol through an apparatus of the De Vilbiss type No. 40.

The guinea pigs were subjected to experiments with sensitization to egg albumin and aerosols with histamine.

- (A) Experiments with guinea pigs sensitized to egg albumin. The animals were sensitized with two injections of egg white, crude, sterile, diluted 1/10 (0.25 ml intraperitoneally, with 5 days interval). Guinea pigs were divided in 2 groups:

- (1) Group of 7 guinea pigs previously treated with *Prednisone* and submitted to an aerosol of a solution of egg albumin 1/100;
- (2) Control group of 6 guinea pigs, without previous treatment with *Prednisone* and submitted to the same aerosol of egg white.
Prednisone was given by a thin and flexible stomach tube, in the following doses: 5 mg in the 19th day after the second sensitizing injection; 7.5 mg in the 20th, 21st and 23rd days; 10 mg in the 24th day, four hours before the challenge nebulization.

- (B) Experiments with aerosols of histamine.

Guinea pigs were divided in two groups:

- (1) Group of 6 animals previously treated with *Prednisone*, as above described, and submitted to an aerosol of histamine dihydrochlorid at 1/100.

- (2) Control group of 5 normal guinea pigs, submitted to an aerosol of histamine dihydrochlorid at 1/100.

RESULTS

In the first group (A), of guinea pigs sensitized to egg albumin, the result was as follows: In the group previously treated with *Prednisone*, only 2 guinea pigs showed tachypnoea after 10–11 minutes. The same animals, submitted to the same experiment after 7 days, gave the following result: 4 guinea pigs showed typical attacks of fatal asthma, respectively 2–3 and 10 minutes after nebulization; 2 guinea pigs showed tachypnoea and 1 guinea pig had no symptoms.

In the control group, not treated with *Prednisone*, all guinea pigs had typical attacks of asthma, with convulsions 1–2 minutes after the nebulization.

The second group (B) of guinea pigs, treated with the same dose of *Prednisone* and submitted to an aerosol of histamine, gave following result: 5 animals showed dyspnoea and convulsions after 60–70 seconds. The control group, not treated with *Prednisone*, showed dyspnoea and convulsions after 50–120 seconds.

DISCUSSION

The effect of *Prednisone* upon those guinea pigs sensitized with egg albumin seems to have been an obvious one, since the drug inhibited experimental asthma. Only 2 guinea pigs presented tachypnoea, after 10–11 minutes of nebulization. There was, thus, a sharp contrast with the control group, not treated *Prednisone*. All of the 6 guinea pigs from this control group manifested fatal asthma after 1–2 minutes. With the suppression of *Prednisone*, it was noted, after 7 days, that its inhibiting effect upon asthma had nearly disappeared, for most guinea pigs had typical asthma or tachypnoea after 2–3 minutes; only one guinea pig presented no symptoms at all.

The inhibiting effect of *Prednisone* upon experimental

asthma,—due to an aerosol of egg albumin—can be discussed in the same way as was done by several authors, using ACTH or cortisone. *Feinberg & Malkiel* (5) demonstrated the inhibiting action of these hormones upon asthma of passively sensitized guinea pigs.

Cortisone and ACTH do not protect guinea pigs against common direct anaphylaxis, but they inhibit a definite proportion of inverse anaphylactic shock with Forsman antigen, *Arbesman* (1). *Feinberg et al.* (16) confirmed the inhibiting effect of ACTH, cortisone, Pyribenzamine, localized chemical inflammation, sodium nucleate and human serum against guinea pig asthma elicited by aerosol antigens. This effect could be partially explained by the stimulus of the pituitary-adrenalaxis, according to the concepts of *Selye* (22). Bilateral adrenalectomy, however, does not prevent the inhibiting effect of sodium nucleate upon experimental asthma; *Benain et al.* (2) admit that such "stress" is not mediated—by the pituitary-adrenocortical stimulation.

Herxheimer & Rosa (12) demonstrated that ACTH or cortisone, when administered during the period of antibody formation, resulted in a prolonged reaction time, when the animals were exposed to aerosol; they explain this fact by the interference of these hormones with antibody formation.

Considerable work has been done about the relationship between cortisone and ACTH, and liberation of histamine, but the reports do not always agree.

In our experiments, *Prednisone* did not protect guinea pigs against bronchospasm induced by aerosol of histamine, since the animals died with asphyxic convulsions, within 60–70 seconds after starting the nebulization; this period was the same as in the control group. Identical observations were made by *Feinberg et al.* (5), using ACTH and cortisone.

According to *Carryer & Code* (4), *Friedlaender & Friedlaender* (7), *Schild et al.* (20), there is no evidence that ACTH and cortisone inhibit liberation of histamine under experimental conditions or that they affect its action once it has been released. These hormones apparently do not interfere

on the action of histamine, introduced into the body or already liberated, but they seem to inhibit the biogenesis of histamine. Later assumption was confirmed by some experiments of *Selye* and *Halpern*. *Selye* (21) mentioned that cortisone and ACTH inhibit anaphylactoid reactions of the rat, due to parenteral administration of egg white, which were greatly assigned to liberation of histamine (*Rocha e Silva*) (19). *Halpern* (9) thinks that cortisone inhibits the biogenesis of histamine; this is demonstrated by the depletion of histamine after successive liberations induced by Dextran.

Rocha e Silva (19) believes certain polysaccharides are able to activate the potency of the histamine provoking agent (anaphylotoxin), which exists in the blood, so that the favorable effect of the adrenocorticoids may be due to interference upon the mechanism of anaphylotoxin activation.

Besides these possible ways of action, ACTH and cortisone can modify unspecifically the capillary permeability. *Benditt et al.* (3) noted that the previous administration of these hormones for 5 days inhibits the signs of increased capillary permeability, produced by hyaluronidase. Similar observations were made by *Hayes et al.* (11). The "spreading activity" of hyaluronidase is partially prevented by antihistaminics (*Mayer*) (16).

Notwithstanding the great amount of work done on the subject, there are only some hints that adrenocortical hormones inhibit the biogenesis of histamine and that, probably, they do not influence the effects of histamine which has already been released, excepting, perhaps, those effects due to disturbances of capillary permeability.

SUMMARY

(1) *Prednisone*, given orally, in daily amounts of 5 to 10 mg, during the last 6 days of sensitization, inhibits experimental asthma of the guinea pig, produced by egg white.

(2) A similar inhibiting effect was not verified, with the

same amounts of *Prednisone*, upon bronchospasm of the guinea pig, elicited by aerosol of histamine.

(3) The exact way of action of this hormone upon these types of reaction is not sufficiently clear, but several possibilities are discussed.

BIBLIOGRAPHY

1. *Arbesman, C. E., Neter, E. & Bertram, L. P.*: The effect of ACTH and cortisone on certain immunologic mechanisms including reversed anaphylaxis. *J. Allergy*, 22, 340, 1951.
2. *Benain, C., Feinberg, S. M. & Sternberger, L. A.*: "Stresses" and hypersensitivity. Effect of adrenalectomy in the guinea pig on asthma from antigen and histamine aerosols and on its inhibition by a nonspecific substance, sodium nucleate. *J. Allergy*, 26, 481, 1955.
3. *Benditt, E. P., Schiller, S., Wong, H. & Dorfman, A.*: Influence of ACTH and cortisone upon alteration in capillary permeability induced by hyaluronidasis in rats. *Proc. Soc. Exp. Biol. & Med.*, 75, 782, 1950.
4. *Carrier, H. M. & Code, C. F.*: Release of histamine during hemolytic reactions in blood of rabbits. *Proc. Soc. Exp. Biol. & Med.*, 73, 452, 1950.
5. *Feinberg, S. M. & Malkiel, S.*: Protective effect of cortisone on induced asthma in the guinea pig. *Proc. Soc. Exp. Biol. & Med.*, 81, 104, 1952.
6. *Feinberg, S. M., Malkiel, S. & McIntire, F. C.*: The effect of stress factors on asthma induced in guinea pigs by aerosolised antigens. *J. Allergy*, 24, 302, 1953.
7. *Friedlaender, S. & Friedlaender, A. S.*: Effect of pituitary adrenocorticotrophic hormone (ACTH) on histamine intoxication and anaphylaxis in guinea pig. *J. Allergy*, 21, 303, 1950.
8. *Germuth Jr., F. G., Oyama, J. & Ottinger, B.*: Mechanism of action of 17-hydroxy-11-dehydrocorticosterone (compound E) and of adrenocorticotrophic hormone in experimental hypersensitivity in rabbits. *J. Exp. Med.*, 94, 139, 1951.
9. *Halpern, B.*: In Histamine. London, J. A. Churchill, 1956.
10. *Harris, S. & Harris, T. N.*: Effect of cortisone on some reactions of hypersensitivity in laboratory animals. *Proc. Soc. Exp. Biol. & Med.*, 74, 186, 1950.
11. *Hayes, M. A. & Brigman, R. M.*: Dermal spreading of hyaluronidase as influenced by prolonged local treatment with certain steroid hormones. *Proc. Soc. Exp. Biol. & Med.*, 77, 597, 1951.
12. *Herxheimer, H. & Rosa, L.*: The action of cortisone in the anaphylactic shock of the guinea pig. *J. Physiol.*, 118, 7, 1952.
13. *Kallos, P. & Pagel, W.*: Experimentelle Untersuchungen über Asthma bronchiale. *Acta med. Scandinav.*, 91, 292, 1937.

14. *Leger, J., Leith, W. & Rose, B.*: Effect of adrenocorticotrophic—hormone on anaphylaxis in the guinea pig. *Proc. Soc. Exp. Biol. & Med.*, 69, 465, 1948.
15. *Malkiel, S.*: The influence of ACTH and cortisone on histamine and anaphylactic shock in the guinea pig. *J. Immunol.*, 66, 379, 1951.
16. *Mayer, R. L.*: Antihistamine agents in allergy; activity of pyribenzamine and related compounds with special reference to their mode of action. *Ann. New York Acad. Sc.*, 50, 1, 127, 1950.
17. *Rather, B.*: Temporal and quantitative factors influencing the development of experimental asthma in the guinea pig. *J. Allergy*, 24, 316, 1953.
18. *Rich, A. R., Berthrong, M. & Bennett Jr., I. L.*: The effect of cortisone upon the experimental cardiovascular and renal lesions produced by anaphylactic hypersensitivity. *Bull. John's Hopkins Hosp.*, 87, 549, 1950.
19. *Rocha e Silva, M.*: Histamine.—Its role in anaphylaxis and allergy. Springfield, Charles C. Thomas, 1955.
20. *Schild, H. O., Hawkins, D. F., Mongar, J. L. & Herxheimer, H.*: Reaction isolated human asthmatic lung and bronchial tissue to specific antigen; histamine release and muscular contraction. *Lancet*, 11, 376, 1951.
21. *Selye, H.*: Effect of ACTH and cortisone upon an "Anaphylactoid reaction". *Canad. Med. Assoc. J.*, 61, 553, 1949.
22. — Stress. Acta Inc., Montreal, 1950.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.